



Summary of Grading of Recommendations Assessment, Development and Evaluation (GRADE) of herpes zoster vaccines

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Background

- Two separate GRADE assessments were performed for herpes zoster subunit vaccine (HZ/su) and live attenuated herpes zoster vaccine (ZVL, Zostavax™)
- The results were presented to the Advisory Committee on Immunization Practices (ACIP) on February 22, 2017 and June 21, 2017, respectively

GRADE Process

- **Develop policy questions**
- **Consider critical outcomes**
- **Review and summarize evidence of benefits and harms**
- **Evaluate quality of evidence**
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- ACIP recommendation and GRADE category

Outcome measures included in evidence profile

OUTCOME	IMPORTANCE
Benefits	
Prevent herpes zoster	Critical
Prevent postherpetic neuralgia (PHN)	Critical
Duration of protection	Important
Harms	
Serious adverse events	Critical
Reactogenicity	Important

GRADE of herpes zoster subunit vaccine (HZ/su)

Policy Question: Should Herpes Zoster subunit vaccine (HZ/su) be routinely used to prevent herpes zoster?

Population	Immunocompetent adults aged 50 years or older
Intervention	2 doses of HZ/su (50 µg gE/AS01 _B) administered intramuscularly at 0 and 2 months
Comparison	Placebo or no vaccine
Outcomes	Herpes zoster (HZ) Post herpetic neuralgia (PHN) Duration of protection against herpes zoster Severe adverse events Reactogenicity [Grade 3 rxn]

Estimates of effects: Benefits, HZ/su

- Prevention of herpes zoster

Age	No. of subjects (# studies)	Vaccine efficacy (95% CI)
50-59 y	7,017 (1)	96.6% (89.6, 99.3)
60-69 y	4,307 (1)	97.4% (90.1, 99.7)
70-79 y	13,022 (1)	91.3% (86.0-94.9)
≥ 80 y	3,574 (1)	91.4% (80.2-97.0)

- Prevention of PHN

Age	No. of subjects (# studies)	Vaccine efficacy (95% CI)
≥ 50y	27,916 (1)	91.2% (75.9-97.7)
≥ 70y	16,596 (1)	88.8% (68.7-97.1)

- Duration of protection (herpes zoster): VE maintained ≥ 85% four years post vaccination

Estimates of effects: Harms, HZ/su

- Serious adverse events and reactogenicity (grade 3 rxn)

ZOE-50/70	No. of subjects (# studies)	No. reported in controls (%)	No. reported in vaccinated (%)	Difference
Serious adverse event	29,311 (1)	1,900 (13.0%)	1,842 (12.6%)	0.4%
Serious adverse events considered related to vaccine	29,311 (1)	15(0.1%)	15 (0.1%)	0.0%
Any Grade 3 reaction	9,936 (1)	155 (3.1%)	820 (16.5%)	13.4%
Injection-site reaction	9769 (1)	17 (0.3%)	460 (9.4%)	9.1%
Systemic reaction	9762 (1)	116 (2.4%)	528 (10.8%)	8.4%

- The remaining 7 studies administered HZ/su to a total of 616 participants and found no SAEs related to vaccination and similar rates of reactogenicity as reported above

GRADE Summary

Comparison: 2 doses of HZ/su (50 µg gE/A S01B) versus placebo in adults ≥50

Outcome	Design (# of studies)	Findings	Evidence type	Overall evidence type
CRITICAL				
Prevent herpes zoster	RCT (1)	HZ/su significantly efficacious in preventing herpes zoster	1	
Prevent post-herpetic neuralgia	RCT (1)	HZ/su significantly efficacious in preventing PHN	1	1
Severe adverse events	RCT (2) RCT* (4) Non-RCT (2)	No differences detected between vaccinated and comparison populations for serious adverse events	1	
IMPORTANT				
Reactogenicity (Grade 3 rxn)	RCT (2) RCT* (4) Non-RCT (2)	Grade 3 reactions more commonly reported in vaccinated groups compared to placebo	1	
Duration of protection (herpes zoster)	RCT (1)	HZ/su significantly efficacious in preventing herpes zoster 4 years post last vaccination	1	

GRADE of live attenuated herpes zoster vaccine (ZVL)

Policy Question: Is the live attenuated herpes zoster vaccine (ZVL) safe and effective at preventing herpes zoster?

Population	Immunocompetent adults aged 50 years or older
Intervention	One dose live attenuated zoster vaccine (ZVL, PFU \geq 19,400)
Comparison	Placebo or no vaccine
Outcomes	<ul style="list-style-type: none">• Herpes zoster (HZ)• Post herpetic neuralgia (PHN)• Duration of protection against herpes zoster (4+ years post vaccination)• Severe adverse events• Reactogenicity (injection-site or systemic reactions)

Estimates of effects: Benefits, ZVL

- Prevention of herpes zoster
 - Vaccine efficacy against herpes zoster, clinical trial data: VE [95% CI]
 - 50-59y: 70% [54-81]
 - 60-69y: 64% [56-71]
 - 70-79y: 41% [28-52]
 - ≥80y: 18% [-29-48]
 - VE from observational studies in adults ≥60y ranged from 33% to 51% (within 4 years post vaccination)
- Prevention of PHN
 - Vaccine efficacy against herpes zoster, clinical trial data: VE [95% CI]
 - 60-69y: 65.7% [20.4-86.7]
 - ≥70y: 66.8% [43.3-81.3]
 - VE from observational studies in adults ≥60y ranged from 41% to 69% (within 4 years post vaccination)
- Duration of protection (herpes zoster):
 - ZVL effectiveness drops after the first year post vaccination and continues to decline year by year.
 - Beyond 4 years, all studies estimates VE ≤40% after 4 years post vaccination

Estimates of effects: Harms, ZVL

- Serious adverse events
 - In 8 placebo-controlled RCTs with 36,868 participants receiving ZVL, there were no imbalances in serious adverse events between vaccine and placebo groups*
 - 20 additional studies with no comparison groups that found no serious adverse events associated with ZVL
- Reactogenicity
 - One large RCT in adults \geq 60y reported injection-site reactions among 48% of vaccine recipients compared to 17% among placebo [diff=31%; Oxman, 2005]
 - Similar rates reported in other clinical studies
 - 4 studies reported Grade 3 injection-site reactions that ranged between 0%-4% of vaccine recipients
 - 7 studies reported vaccine-related systemic adverse events, with reactions reported among 0-8% of vaccine recipients
- Several cases of PCR-confirmed VZV rash caused by Oka/Merck strain were reported in clinical trials and Merck's 10 year post-marketing review [FDA; Willis, 2016]

*In the Shingles Prevention Study adverse event substudy, significantly more subjects in the vaccine group had serious adverse events than in the placebo group (1.9% vs. 1.3%, respectively; P=0.03); A post hoc, subject-by-subject review found no clinically meaningful differences between the groups in the pathophysiology, nature, timing, intensity, or outcome of these events. (Oxman, NEJM, 2005)

GRADE Summary

Comparison: One dose ZVL ($\geq 9,000$ PFU) versus placebo or no vaccine in adults ≥ 50

Outcome	Design (# of studies)	Findings	Evidence type	Overall evidence type
CRITICAL				
Prevent herpes zoster	RCT (2) Obs (7)	ZVL is effective in preventing herpes zoster	1	1
Prevent post-herpetic neuralgia	RCT (3) Obs (5)	ZVL is effective in preventing PHN	1	
Severe adverse events	RCT (14) Non-RCT (6) Obs (7)	No safety concerns for ZVL observed in real-world and clinical settings	1	
IMPORTANT				
Reactogenicity	RCT (15) Non-RCT (5) Obs (5)	Injection-site reactions more commonly reported among vaccine recipients compared to placebo, but tend to be mild	1	2
Duration of protection (herpes zoster)	RCT (2) Obs (3)	ZVL effectiveness drops after the first year post vaccination and continues to decline year by year	2	

Conclusion

- GRADE analyses were performed separately for the two existing herpes zoster vaccines – HZ/su and ZVL
- For both vaccines, the evidence type for criterial outcomes is 1.
- We have high confidence in the estimates of effect for these outcomes for both vaccines.

Thank You

For more information, contact CDC
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